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| EXAMINER | |
|---|---|
| SASAN, ARADHANA | |
| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/664,803 | KOSITPRAPA ET AL. | |
| | Examiner | Art Unit | |
| | ARADHANA SASAN | 1615 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *35,37,39,40,42,44 and 47-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35, 37, 39, 40, 42, 44 and 47-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/04/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application*

1. The remarks and amendments filed on 06/15/09 are acknowledged.

2. Claims 1-34, 36, 38, 41, 43, and 45-46 were cancelled.

3. New claims 47-51 were added.

4. Claims 35, 37, 39, 40, 42, 44, and 47-51 are included in the prosecution.

### *Information Disclosure Statement*

5. The information disclosure statements (IDS) submitted on 06/04/09 are acknowledged. The submissions are in compliance with the provisions of 37 CFR 1.97 and 1.98. Accordingly, the examiner is considering the information disclosure statements.

See attached copy of PTO-1449.

### *Response to Arguments*

**Claim Objection**

6. In light of the amendment of claim 35, the objection with respect to this claim is withdrawn.

## MAINTAINED REJECTIONS:

The following is a list of maintained rejections:

### *Claim Rejections - 35 USC § 103*

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 35, 37, 39, 40, 42 and 44 **remain** rejected and **new claims 47-51** are rejected under 35 U.S.C. 103(a) as being unpatentable over Cutie et al. (WO 01/82875), in view of Lewis (WO 01/35940) and further in view of Vergez et al. (US 2006/0204578).

The claimed invention is a once a day oral pharmaceutical tablet consisting essentially of:

(a) a controlled release metformin core consisting essentially of:

(i) a compressed mixture of

(A) 50-98% of metformin hydrochloride;

(B) 0.1-40% of a binding agent;

( C) 0-20% of an absorption enhancer; and

(D) 0-5% of a lubricant;

(ii) optionally a secondary seal coat surrounding the metformin mixture and

(iii) a semipermeable membrane surrounding the metformin mixture or the secondary seal coat if present consisting essentially of:

(A) 50-99% of a polymer that is permeable to the passage of water and aqueous biological fluids and is impermeable to the passage of metformin;

(B) 0-40% of a flux enhancer and

( C) 0-25% of a plasticizer, said membrane having at least one passageway formed therein for release of the metformin;

(b) a primary seal coat that does not contain an active pharmaceutical ingredient, that rapidly disperses or dissolves in water and that is applied to the semipermeable membrane of the controlled release core; and

(c) an immediate release pioglitazone coating applied to the primary seal coat consisting essentially of:

(i) pioglitazone hydrochloride;

(ii) a binder; and

(iii) a pore former.

The tablet exhibits the following metformin dissolution profile when tested in a USP Type 2 apparatus at 75 rpms in 900 ml of simulated intestinal fluid and 37°C: 20-40% of the metformin is released after four hours; 45-90% of metformin is released after eight hours. The dosage form exhibits the following pioglitazone dissolution profile when tested in a USP apparatus Type 1 apparatus at 100 rpm in a pH 2.0 HCl-0.3M KCl buffer solution: at least 79% of the pioglitazone is released after 20 minutes and at least 95% of the pioglitazone is released from the tablet after 30 minutes.

Cutie teaches a "core formulation comprising a first layer comprising pioglitazone, which covers at least a portion of a core comprising the biguanide, metformin (i.e. glucophage)" (Page 1, lines 6-7). A core of the metformin is formed and a layer of pioglitazone hydrochloride is deposited on the core (Page 10, claim 8). This reference teaches that "the first layer should comprise pioglitazone hydrochloride because its dose requirement is lower compared to metformin. Additionally, it is slightly non-polar, its solubility rate slower, and its absorption rate thus dependent on its

dissolution rate in the contents of the gastrointestinal tract compared with metformin" (Page 2, lines 26-30). The "core formulation ... is preferably fabricated by compression into a tablet" (Page 6, lines 15-16). The core formulation may be coated with sugar, shellac or other enteric coating agents (Page 7, lines 9-11). Cutie teaches that the core formulation can have an outer shell made of a biodegradable material (including cellulosic polymers, polyvinyl acetate, and polyvinyl alcohol) (Page 7, lines 13-28).

Cutie does not expressly teach a primary seal coat that does not contain an active pharmaceutical ingredient, that rapidly disperses or dissolves in water and that is applied to the controlled release core.

Lewis teaches a pharmaceutical composition comprising a thiazolidinedione that is formulated as a thin layer upon the surface of the metformin hydrochloride (Page 1, lines 30-35). The metformin hydrochloride is in a compacted form, such as a tablet and the composition also comprises an inert barrier layer between the layer containing thiazolidinedione and the metformin hydrochloride (Page 1, lines 36-39).

Cutie and Lewis do not expressly teach a semipermeable membrane.

Vergez teaches a controlled release osmotic device of two or more different active agents where the "core is surrounded by a membrane having at least one or two preformed holes. The first pharmaceutical composition provides a controlled release of a first active agent through its respective first preformed passageway(s) in the semipermeable membrane. The second pharmaceutical composition provides a controlled release of a second active agent through a respective second passageway(s) in the semipermeable membrane. Both layers deliver their respective active agent

through osmotic pumping" (Page 2, [0015]). Semipermeable membrane materials including cellulose acetates, flux enhancing agents (PEG 400), and plasticizers are disclosed (Page 10, [0109]).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a core of the metformin and deposit a layer of pioglitazone hydrochloride on the core, as taught by Cutie, combine it with a composition comprising an inert barrier layer between a layer containing thiazolidinedione and metformin hydrochloride, as taught by Lewis, further combine it with the osmotic controlled release device comprising a semi permeable membrane, as taught by Vergez, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because the inert barrier layer taught by Lewis protects the inner core comprising metformin hydrochloride, thereby enhancing the controlled release properties of the metformin hydrochloride and osmotic devices with semipermeable membrane components (such as cellulose polymers, flux enhancing agents and plasticizers) are known in the art, as evidenced by the osmotic controlled release device of Vergez.

Regarding instant claim 35 and new claim 47, the limitation of "once a day oral" dosage form denotes a future-intended use and thus, does not accord patentable weight to the claims. The limitation of the controlled release metformin core would have been obvious over the core of metformin taught by Cutie (Page 1, lines 6-7 and Page 10, claim 8) and Lewis (Page 1, lines 30-35). The limitation of the primary seal coat that does not contain an active pharmaceutical ingredient would have been obvious over the

coating of the core with sugar, shellac or other enteric coating agents as taught by Cutie (Page 7, lines 9-11), in view of the inert barrier layer between the layer containing thiazolidinedione and the metformin hydrochloride, as taught by Lewis (Page 1, lines 36-39). The limitation of the immediate release pioglitazone coat would have been obvious over the layer of pioglitazone hydrochloride on the core of metformin as taught by Cutie (Page 10, claim 8), in view of the thiazolidinedione that is formulated as a thin layer upon the surface of the metformin hydrochloride core as taught by Lewis (Page 1, lines 30-35). The limitation of the dissolution profile of the dosage form would have been obvious over the dosage form disclosed by Cutie that includes pioglitazone hydrochloride from 1mg to 45mg and metformin from 100mg to 2550mg (Page 3, lines 7-9). One with ordinary skill in the art would use the standard dissolution procedures from the USP to test the in vitro dissolution profile of the formulation of a core of metformin with a layer of pioglitazone hydrochloride. Since the metformin is in the controlled release core and the pioglitazone is in the immediate release portion of the dosage form (as taught by Cutie), long term release of the metformin (even after 8 hours) and short term or immediate release of the pioglitazone (after 30 minutes) would be obvious to one of ordinary skill in the art. The semipermeable membrane would have been obvious over the semipermeable membrane taught by Vergez (Page 10, [0109]). The limitation of the release of pioglitazone as tested in a USP apparatus would have been obvious over the dosage form disclosed by Cutie that includes pioglitazone hydrochloride from 1mg to 45mg and metformin from 100mg to 2550mg (Page 3, lines 7-9). One with ordinary skill in the art would use standard dissolution procedures from

the USP to test the in vitro dissolution profile of the formulation of a core of metformin with a layer of pioglitazone hydrochloride. Since the pioglitazone is in the immediate release portion of the dosage form (as taught by Cutie), short term or immediate release of the pioglitazone (after 20 minutes and after 30 minutes) would have been obvious to one of ordinary skill in the art. The pore former would have been obvious over the PVP taught by Lewis (Page 7, Example 1, line 14). The limitation of the tablet would have been obvious over the controlled release core of metformin that may contain "binders such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel®, corn starch ... a lubricant such as magnesium stearate ..." as taught by Cutie (Page 6, line 33 to Page 7, line 3). One with ordinary skill in the art would know that osmotic tablets are generally used for controlled or sustained release of active ingredients. One with ordinary skill in the art would know that osmotic tablets contain components such as binders and disintegrating agents that promote the gradual break down of the tablet that subsequently allows for controlled or sustained release.

Regarding instant claim 37 and new claims 49-51, the limitation of 75-95% of metformin in the core would have been obvious over the 500mg of metformin HCl in the core (calculated percent: 500mg/520mg = 96.15% of granules) as taught by Lewis (Page 7, lines 10-13). The limitation of 3-15% of a binding agent would have been obvious over the 15mg of polyvinylpyrrolidone (calculated percent: 15mg/520mg = 2.88% of granules) as taught by Lewis (Page 7, Example 1, line 14). The limitation of 0.5-1% of a lubricant would have been obvious over the 5mg of magnesium stearate

(calculated percent: 5mg/520mg = 0.96%) as taught by Lewis (Page 7, Example 1, line 15). The secondary seal coat surrounding the coat would have been obvious over the inert barrier layer between the layer containing thiazolidinedione and the metformin hydrochloride, as taught by Lewis (Page 1, lines 36-39). The semipermeable membrane would have been obvious over the semipermeable membrane taught by Vergez (Page 10, [0109]). The limitation of 50-99% of a polymer would have been obvious over the cellulose acetate (calculated percent: 19.05mg/20mg = 95.25%), polyethylene glycol 400 (calculated percent: 0.95mg/20mg = 4.75%) as taught by Vergez (Page 17, Example 1, Table - Coating A). The limitation of at least one passageway would have been obvious over the passageway in the semipermeable membrane as taught by Vergez (Page 2, [0015]).

Regarding instant claim 39, the limitation of the release of metformin that is not regulated by an expanding polymer would have been obvious over the core comprising metformin which does not contain an expanding polymer, as taught by Cutie (Page 10, claim 8).

Regarding instant claim 40, the limitation of the Tmax of metformin would have been obvious over the dosage form disclosed by Cutie that includes metformin from 100mg to 2550mg (Page 3, lines 7-9). One with ordinary skill in the art would administer the dosage form and measure the peak plasma levels of metformin. Controlled release is generally known to delay the release of an active ingredient. Since the metformin is sequestered in the controlled release core, it would have been obvious that the Tmax would range from 8-12 hours.

Regarding instant claim 42, the limitation of the Tmax of the pioglitazone would have been obvious over the dosage form disclosed by Cutie that includes pioglitazone hydrochloride from 1mg to 45mg (Page 3, lines 7-9). One with ordinary skill in the art would administer the dosage form and measure the peak plasma levels of the thiazolidinedione. Immediate release is generally known to hasten the release of an active ingredient. Since the pioglitazone is present in the immediate release layer, it would have been obvious that the Tmax would range from 1-12 hours.

Regarding instant claim 44 and new claim 48, the limitation the pioglitazone coating by using a solvent mixture of water and an organic solvent obvious over the shell (comprising the pioglitazone) that is obtained by conventional microencapsulation process (Page 7, line 31 to Page 8, line 5). One of ordinary skill in the art would use a solvent or a mixture of solvents based on the desired encapsulation of pioglitazone and the recited mixture of water and an organic solvent would have been an obvious variant of the processes cited by Cutie.

***Response to Arguments***

9. Applicant's arguments, see Page 7, filed 06/15/09, with respect to the rejection of claims 35-46 under 35 USC § 103(a) as being unpatentable over Cutie et al. (WO 01/82875), in view of Lewis (WO 01/35940) and further in view of Vergez et al. (US 2006/0204578) have been fully considered but are not persuasive.

Applicant argues that Cutie does not disclose or suggest coating the metformin core with a modified release coating and applying an immediate release pioglitazone coating to a seal coated modified release metformin core. Applicant argues that the

Examiner is incorrectly interchanging the terms "core" and "core formulation" as used in Cutie. Applicant points out the definition of the "core formulation" in Cutie (Page 1, lines 6-8 and Page 3, lines 3-6) and states that Cutie is instructing the skilled artisan to coat both the metformin and pioglitazone with these coatings.

This is not persuasive because the application of a layer of pioglitazone HCl on an inner "core" of metformin is clearly taught by Cutie (Page 10, claim 8). The teaching of Cutie is combined with the composition comprising an inert barrier layer between an outer thiazolidinedione layer and an inner compacted core containing metformin HCl ((Page 1, lines 30-39). One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that the addition of Lewis and/or Vergez does not overcome the deficiencies of Cutie. Applicant argues that the combination of Cutie with Vergez would result in a dosage form wherein both the metformin and pioglitazone are released in a controlled manner and not a dosage form wherein the metformin is released in a controlled manner and the pioglitazone in an immediate release manner as required by the pending claims.

This is not persuasive because Vergez is used as a supporting reference that provides the teaching of a semi permeable membrane as applied in an osmotic controlled release device. Vergez can be properly combined with Lewis and Cutie because the semi permeable membrane of Vergez allows controlled release of an

active agent. One of ordinary skill in the art would use the semi permeable membrane of Vergez with the controlled release metformin core of Cutie in order to further control the release of metformin from the dosage form. One of ordinary skill in the art would have a reasonable expectation of success in producing a functional dosage form with controlled release of metformin from the core and immediate release of pioglitazone from the outer layer/coating.

Therefore, the rejection of 03/13/09 is maintained.

***Double Patenting***

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 35, 40 and 42 **remain** provisionally rejected and **new claims 47-51** are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 20, 33 and 37-38 of copending Application No. 11/094,493 ('493 hereinafter). Although the conflicting claims are not identical, they are not

patentably distinct from each other because both applications describe a controlled release core comprising metformin and an immediate release thiazolidinedione derivative containing component comprising pioglitazone. The difference is that instant claims are drawn to an immediate release thiazolidinedione containing coating and claims of '493 are drawn to an immediate release thiazolidinedione containing "component". It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare an immediate release component in the form of an immediate release coating with a thiazolidinedione. The same ranges for peak plasma levels (Tmax) of the pioglitazone are recited in instant claims and in claims of '493.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Response to Arguments***

12. Applicant's arguments, see Page 12, filed 06/15/09, with respect to the provisional rejection of claims 35, 36, 38, and 40-42 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 20, 33 and 37-38 of copending Application No. 11/094,493 have been fully considered but are not persuasive.

Applicant state that once allowable subject matter is found in either application, Applicant will consider submitting a terminal disclaimer if appropriate.

Until such time that a terminal disclaimer is filed and approved, this rejection will be maintained and applied to new claims 47-51.

***New claims 47-51***

13. Applicant's a amendment introduced new claims 47-51 which are included in the rejections above. Since the new ground(s) of rejection for claims 47-51 were necessitated by Applicant's amendment this action is made FINAL.

***Conclusion***

14. No claims are allowed.

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/
Examiner, Art Unit 1615

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615